REMARKS

Following entry of the foregoing amendments, claims 1, 4, 9, 101, and 110 to 114 will be pending in this patent application. Claims 1 and 4 have been amended, and claims 5, 6, 21, 24, 25, 36, and 37 have been canceled, herein, without prejudice. New claims 110 to 114 have added. Support for the amendments and for new claims 110 to 114 is found throughout the specification of priority application number 08/870,608 as originally filed, as discussed at length below. The amendments and claims 110 to 114 thus do not introduce new matter into the application.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Priority

The present application claims priority to U.S. patent application number 08/870,608 ("the 608 application"). The compositions recited in the claims as amended herein are fully supported by the 608 application, and the claims are therefore entitled to the benefit of the June 6, 1997 filing date of the 608 application.

Claim 1 has been amended herein to recite compositions that comprise a complementary pair of siRNA oligomeric compounds consisting of a first oligomeric compound and a second oligomeric compound. The first and second oligomeric compounds are not covalently linked to each other. At least a portion of the first oligomeric compound is complementary to at least a portion of the second oligomeric compound and to a target nucleic acid. And at least one of the first and second oligomeric compound comprises a conjugate group.

Claim 4 has been amended herein to recite that each of the first and second oligomeric compounds comprises 17 to 25 nucleotides.

New claim 110 recites that the first oligomeric compound comprises a 5' region comprising 2'-OCH_3 modified nucleosides, a central region comprising β-D-ribonucleosides, and a 3' region comprising 2'-OCH_3 modified nucleosides. New claim 111 recites that the

nucleosides in the 5' and 3' regions of the first oligomeric compound are joined by phosphorothioate linkages, and new claim 112 recites that the nucleosides in the central region of the first oligomeric compound are joined by phosphorothioate linkages.

New claim 113 recites that the second oligomeric compound comprises a 5' region comprising nucleosides joined by phosphorothioate linkages, a central region comprising β-D-ribonucleosides; and a 3' region comprising nucleosides joined by phosphorothioate linkages. And new claim 113 recites that the 5' and 3' regions of the second oligomeric compound each independently comprise 2'-OCH_3 modified nucleosides.

Support for these claims is found throughout the specification of the 608 application as originally filed, for at least the following reasons.

According to the M.P.E.P., "the fundamental factual inquiry [underlying the written description requirement] is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed.[1] The M.P.E.P. further states that the "subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement."[2] And to make a determination regarding the adequacy of the disclosure, the entire specification must be considered.[3] If the specification of the 608 application *as a whole* were considered by one skilled in the art, it would be readily apparent that applicants were in possession of the compositions recited in the claims as amended herein at the time the 608 application was filed.

For example, Example 27-a of the 608 specification describes duplexes comprising a "sense strand" and an "antisense strand,"[4] and refers to the strands of such duplexes as "oligoribonucleotides."[5] Original claims 78 and 79 of the 608 specification also recite duplexes having "a first oligonucleotide and a second oligonucleotide" that comprise various modifications. The description provided in the 608 specification thus demonstrates that

[1] M.P.E.P. § 2163.02 (quoting *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed, Cir. 1991)).
[2] *Id.*
[3] M.P.E.P. § 2163, II, A, (2).
[4] 608 specification as originally filed at page 92.
[5] 608 specification as originally filed at example 27-b, page 96; and example 28, at page 99.

applicants were in possession of duplexes comprising first and second strands, in which the strands are referred to as "oligoribonucleotides" or "oligonucleotides," and have certain modifications.

Moreover, the description of "oligomeric compounds" in the 608 specification includes both "oligoribonucleotides and oligoribonucleosides,"[6] and any description in the 608 specification relating to "oligomeric compounds" thus refers to "oligoribonucleotides."

Review of the *entire* specification of the 608 application reveals the types of "oligoribonucleotides," "oligonucleotides," and "oligomeric compounds" that applicants were in possession of at the time of the invention. In this regard, in accordance with use of the term "oligoribonucleotides" in Example 27-a, and use of the term "oligonucleotides" in original claims 78 and 79, any description in the 608 specification using these terms, as well as the term "oligomeric compound," relates to compounds that are single stranded ***or*** part of a duplex. Once the entirety of the 608 specification is so considered, it becomes apparent that compositions comprising the presently claimed duplexes are fully supported by the 608 application, in view of the abundant description of various "oligoribonucleotides," "oligonucleotides," and "oligomeric compounds" provided in the specification.

With respect to the specific features recited in the claims as amended herein, the 608 application specification describes oligonucleotides bound to conjugate groups.[7]

The specification of the 608 application also describes oligonucleotides of the length recited in claim 4. In this regard, the examples and original claims of the 608 specification describe duplexes comprising "oligoribonucleotides" or "oligonucleotides," and the specification expressly indicates that such molecules can be any of a variety of lengths. For example, the specification states that:

> Preferred oligoribonuelcotides and oligoribonucleosides in accordance with this invention preferably comprise from about 5 to about 50 nucleoside subunits. In the context of this invention it is understood that this encompasses non-naturally occurring oligomers as hereinbefore described, having 5 to 50 nucleoside subunits. It is more preferred that

[6] 608 specification as originally filed at, e.g., page 9, lines 17-20.
[7] 608 specification as originally filed at page 26, lines 12 to 16.

> the oligoribonucleotides and oligoribonucleosides of the present invention comprise from about 15 to about 25 nucleoside subunits.[8]

In addition, Example 27-a describes specific, double-stranded oligomeric compounds in which each of the oligonucleotides present in the duplexes is 17 or 20 nucleotides in length. The 608 specification thus describes duplexes comprising oligoribonucleotides having various lengths, and specifically describes oligoribonucleotides having 17 to 25 nucleoside subunits.

Moreover, the 608 specification also includes copious description of oligoribonucleotides, oligonucleotides, and oligomeric compounds having regions of any of a variety of chemical modifications, such as 2'-O-CH_3 modifications:

> In certain preferred oligomeric compounds of the invention, the first or first and third segments of oligomeric compounds are formed of nucleoside subunits that include 2'-substituent groups thereon. In preferred embodiments, the 2'-substituent group includes…C_1-C_{20} alkoxy…Preferred alkoxy substituents include methoxy…[9]

In addition, the 608 application describes oligonucleotides in which such chemical modifications "are located at one or both of the 3' or the 5' termini of the oligomeric compounds. In certain preferred compounds there are from one to about eight nucleoside subunits that are substituted with such substituent groups."[10]

The specification of the 608 application also describes oligonucleotides having modified internucleoside linkages:

> Other preferred oligomeric compounds of the invention include oligoribonucleotides having nucleoside subunits connected by phosphorus linkages including phosphorothioate, 3'-(or 5') deoxy-3' (or 5') thio-phosphorothioate, phosphorodithioate, phosphoroselenate, 3'- (or 5') deoxy phosphinate, borono phosphate, 3'-(or 5') deoxy-3' (or 5') amino phosphoramidate, hydrogen phosphonate, borono phosphate ester, phophoramidate, alkyl or alryl phosphonate, and phosphotriester."[11]

[8] 608 specification as originally filed at page 24, lines 5 to 13.
[9] 608 specification as originally filed at page 8, lines 4 to 10.
[10] 608 specification as originally filed at page 10, lines 1 to 11.
[11] 608 specification as originally filed at page 8, lines 22 to 30.

In addition, the "oligoribonucleotides" in the double-stranded compounds described in Examples 27-a, 27-b, and 28 of the 608 application comprise various combinations of phosphorothioate and 2'-O-CH_3 modifications, and these examples indicate that the chemical modifications to the strands of the duplexes impart increased stability to exonucleases.[12] The experimental examples of the 608 specification thus describe duplexes comprising sense and antisense oligoribonucleotides that comprise combinations of chemical modifications, such as 2'-O-CH_3 and phosphorothioate linkages, that confer nuclease resistance.

Significantly, the 608 specification makes clear that the described chemical modifications are suitable, and even desirable, for double-stranded compounds. For instance, Example 27-a explains that certain chemical modifications make duplexes "more stable to exonuclease digestion,"[13] and the 608 specification indicates that modifications that improve nuclease resistance of an oligonucleotide are advantageous for double-stranded compounds.[14]

Moreover, the specification of the 608 application describes oligomeric compounds that contain a central region of unmodified ribonucleosides, and explains that when such oligomeric compounds are bound to target RNA, the resultant duplexes serve as substrates for RNases that specifically cleave double-stranded RNA.[15] The 608 specification thus describes unmodified ribonucleosides that, when present in an oligomeric compound, render a duplex of the compound and an RNA molecule subject to cleavage by double-strand specific RNases.

The specification of the 608 application, when properly considered in its entirety, therefore provides support for the presently claimed oligomer duplexes, and the present application is therefore entitled to the benefit of the June 6, 1997 filing date of the 608 application.

[12] 608 specification as originally filed at page 92, lines 25-33; and page 99, lines 10-17.
[13] 608 specification as originally filed page 92, lines 25-30; see also page 99, lines 10-17 (describing desirability of stabilized modified oligoribonucleotides in a duplex).
[14] 608 specification as originally filed at, e.g., page 21, lines 16 to 19.
[15] 608 specification as originally filed at page 6, line 34 to page 7, line 4; page 16, line 22 to page 17, line 2; page 18, line 30 to page 19, line 2; and page 26, line 17 to page 27, line 12.

Alleged Obviousness

Claims 1, 4 to 6, 9, 21, 24, 25, 36, 37, and 101 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by U.S. patent application publication number US 2004/0259247 ("the Tuschl application") in view of U.S. patent application publication number US 2004/0054155 ("the Wolf application"), Schwarz, *et al.*, *Molecular Cell*, 2002, 10, 537-548 ("the Schwarz article"), and Manoharan, M., Marcel Dekker, New York, 2001, 391-467 ("the Manoharan chapter"). Applicants respectfully request reconsideration and withdrawal of this rejection because, as discussed above, the present claims are entitled to the benefit of the filing date of the 608 application, which is June 6, 1997. Since this date is before the priority date of the Tuschl and Woolf applications and the publication dates of the Schwarz article and the Manoharan chapter, these references are not available as prior art with respect to the subject application.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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